

Journal of Rehabilitation Research and Development

Rehabilitation R & D Progress Reports 1990

IX. Neurological and Vascular Disorders

A. General

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IX. Neurological and Vascular Disorders

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A. General

[314] Comparison of Treatment Programs for Multiple Sclerosis Rehabilitation

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Sponsor: VA Rehabilitation Research and Development Service (Project #B395-RA)

Purpose—The goal of this project is to examine the effectiveness of interdisciplinary team care compared with standard neurological care for patients with multiple sclerosis (MS). Our main hypothesis is that coordinated care by experienced practitioners will maximize patients' quality of life, and may eliminate preventable complications of MS.

Methodology—Patients with definite or probable MS are evaluated at baseline, 6, and 12 months. Study measures include the Minimal Record of Disability for Multiple Sclerosis (MRD), the Sickness Impact Profile (SIP), patient satisfaction with health care, the Campbell Index of Life Satisfaction, and enumeration of VA and non-VA medical expenditures. Patients at the Portland VA Medical Center will continue to receive comprehensive neurological care. Patients at the Denver VA Medical Center will be treated in an interdisciplinary team clinic, managed by a nurse practitioner case manager. The team carries out a comprehensive evaluation of the patient's physical, psychological, and social status. Realistic care and rehabilitation goals are established, and the nurse practitioner ensures that the plans are effectively carried out.

Progress—A total of 163 patients participated in the study (82 at Denver and 81 at Portland). Thus far, 116 patients completed 6 months of follow-up, and 32 patients completed 12 months of follow-up. The patients were

88% male, with an average age of 49 years. Most (67%) had chronic progressive MS with an average duration of 17.7 years. The average Expanded Disability Status Scale (EDSS) scores were 6.1. Overall, the Portland patients have a slightly more severe degree of MS than do the Denver patients (EDSS 5.9 in Denver and 6.3 in Portland, $p=0.20$). The groups are otherwise quite comparable in the type, duration, and severity of their MS.

Preliminary Results—We found that the patients had 94 total hospitalizations, including 72 directly related to MS. Of the MS-related hospitalizations, 18 were due to potentially preventable problems. The majority of these hospitalizations were due to urinary tract infections with an estimated total cost of \$186,000. This high frequency of preventable hospitalizations points to an area where an interdisciplinary team focused on aggressive rehabilitation of MS patients can have a major functional and cost impact.

We also examined the problem of caregiver burden and found that 49% of patients had a nonprofessional caregiver (24) working with them for an average of 10 years, and spending an average of 43 hours per week in direct care. Since only 15% of our patients are employed, and only 43% of their caregivers are employed, the economic impact of MS on the family unit is considerable. The caregivers had a very high degree of burden, and this correlated especially with psychosocial dysfunction in the patients.

Our preliminary analysis shows a positive effect of the interdisciplinary team on functional outcomes and satisfaction with health care. At 6 months, the average EDDS score declined from 6.08 to 6.28 with no significant difference between Portland and Denver. Examining functional issues, we found that at 6 months, Denver patients fared significantly better than Portland patients. Functional status, as measured by total Incapacity Status Score (ISS), was better in Denver than Portland, even after adjusting for baseline differences (ISS mean scores 20.2 in Denver, 28.9 in Portland, $F=4.95$, $p=0.028$). In 10 of the 16 subscales of the ISS, the Denver group either improved or showed less decline than did the Portland group. Patient satisfaction with health care improved in Denver ($p<0.001$) and declined in Portland ($p=0.041$). These findings give strong support to the concept that an

interdisciplinary team can result in important improvement in MS patient functional status and that further testing of this concept is warranted.

Recent Publications Resulting from This Research

- A Nurse-Managed Multiple Sclerosis Clinic: Improved Quality of Life for Persons with MS. Winters S et al., *Rehabil Nurs* 14(1):13-22, 1989.
- The Team Approach: Two Models for MS Rehabilitation. Burks JS, Gellerman E, Licari P, *Paraplegia News* 43(4):28-30, 1989.
- Care-Giver Burden in Multiple Sclerosis. Prochazka AV, Mitchell W, Licari P, *Clin Res* 38:107A, 1990.
- Health Care Costs of Multiple Sclerosis. Bourdette DN et al., *Neurology (Suppl 1)*40:276, 1990.
- Bladder, Bowel and Sexual Dysfunction in Multiple Sclerosis. Bourdette DN, in *Multiple Sclerosis: Current Status of Research and Treatment*, R.M. Herndon, F.J. Seil (Eds.). New York: Demos Publications (in press).

[315] Neuromuscular Function: Comparison of Symptomatic and Asymptomatic Postpolio Subjects

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Sponsor: *Easter Seal Research Foundation*

Purpose—Our research was designed to compare symptomatic to asymptomatic postpolio individuals to determine if there were differences in muscle strength, endurance, work capacity, perception of exertion during activity, manner in which the muscle compensates for fatigue, or ability of the muscle to recover strength after activity.

Methodology—We studied quadriceps femoris function in 91 individuals: 41 control, 34 symptomatic and 16 asymptomatic postpolio subjects. Isometric muscle strength was measured in the quadriceps muscles. Endurance testing was performed at 40% of maximal volitional contraction (MVC) until the subject was no longer able to maintain the required torque. Work capacity was defined as the product of torque and endurance time. Rating of perceived exertion was determined at regular intervals during the endurance test. Surface electrophysiologic measures (median frequency of the power spectrum, root mean squared EMG) were made to determine the pattern of muscle fatigue. Post-endurance strength testing was also performed at regular intervals for 10 minutes after exhaustion. Following the above testing, quantitative EMG testing of the quadriceps femoris muscle was performed.

Results/Implications—Quantitative EMG demonstrated that the symptomatic postpolio group had evidence of more severe acute poliomyelitis than in the asymptomatic group. Isometric peak torque of the quadriceps was least in the symptomatic group and greatest in the control group. The endurance time was not statistically different among the three groups, although the isometric work capacity was significantly less in the symptomatic group than the other two groups. Rating of perceived exertion and electrophysiologic measures were the same in all three groups during activity. The symptomatic subjects, however, recovered their strength less readily than did control subjects while the asymptomatic subjects recovered their strength in similar fashion to control subjects.

We also studied the effect of pacing (use of intermittent activity) in seven symptomatic postpolio subjects. In this study, the subjects were tested on three separate days at least one week apart. On the first day (constant exercise) the subject performed the strength and endurance testing as described above. On the second test day (quartile study) the subject performed the same isometric work as on the first test day at 40% of MVC, but the isometric exercise was divided into quartiles with 2-minute rest breaks between quartiles. On the third test day (interval exercise) the subject performed 20-second

intervals of isometric exercise at 40% of MVC until either the rating of perceived exertion was greater than 17 (very hard) or 18 intervals of isometric work were performed.

The results of this study demonstrated significantly less evidence of muscle fatigue by rating of perceived exertion as well as by the electrophysiologic measures in both the quartile and the interval studies as compared to the constant exercise study. The relative recovery of strength at 30 seconds after activity was also significantly greater in quartile and interval exercise than for constant exercise. The amount of isometric exercise performed during the interval exercise paradigm was 237% greater than that performed during constant exercise. Thus, symptomatic postpolio subjects were able to perform similar or greater isometric exercise with less evidence of local muscle fatigue by pacing their activity. This evidence highly supports the concept that pacing of activity can be very beneficial in symptomatic postpolio individuals.

Recent Publications Resulting from This Research

- Symptoms and Clinical Impressions of Patients Seen in a Postpolio Clinic. Agre JC, Rodriquez AA, Sperling KB, Arch Phys Med Rehabil 70:367-370, 1989.
- Neuromuscular Function: Comparison of Symptomatic and Asymptomatic Polio Subjects to Control Subjects. Agre JC, Rodriquez AA, Arch Phys Med Rehabil 71:545-551, 1990.
- Correlation of Quantitative Motor Unit Action Potentials with Neuromuscular Variables and Surface Electromyographic Power Spectrum Characteristics in Polio Survivors and Controls. Rodriquez AA, Agre JC, Muscle Nerve (in press).
- Electrophysiologic Study of the Quadriceps Muscles During Fatiguing Exercise and Recovery: A Comparison of Symptomatic Polios to Asymptomatic Polios and Controls. Rodriquez AA, Agre JC, Arch Phys Med Rehabil (in press).
- Neuromuscular Function Remains Stable in Symptomatic and Asymptomatic Polio Survivors at One Year Follow-up. Agre JC, Rodriquez AA, Arch Phys Med Rehabil (in press).
- Rating of Perceived Exertion and Fatigue During Isometric Exercise in Postpolio Subjects. Rodriquez AA, Agre JC, Arch Phys Med Rehabil (in press).

[316] Mechanisms of Damage-Induced Trigeminal Reorganization

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Sponsor: National Institute of Dental Research, National Institutes of Health

Purpose—This research will define the peripheral and central sequelae of trigeminal nerve damage and, in addition, determine whether these consequences can be altered by treatment with neuronal growth promoters such as bovine brain gangliosides. The study is composed of six projects, each of which will examine an aspect of the reorganization which follows transection of the infra-orbital nerve in either adult or neonatal rats.

Project 1 will employ electron microscopic, multiple retrograde tracing, and electrophysiological methods to address issues of ganglion cell survival and reorganization of peripheral connectivity.

Project 2 will use transganglionic tracing and injection of individual, functionally characterized, primary afferents with horseradish peroxidase (HRP) to determine the extent to which nerve damage or inactivation alters the primary afferent innervation of the trigeminal brainstem complex and whether changes in the central arbors of individual axons can be correlated with alterations in their peripheral connectivity.

Project 3 will concentrate on potential changes in the brainstem organization. In these experiments, novel

morphometric techniques will be employed to delineate the effects of both deafferentation and removal of targets upon the survival of trigeminal brainstem neurons.

Project 4 will employ retrograde tracing, electrophysiological, and HRP injection techniques to delineate the effects of nerve damage or inactivation upon the morphology, response properties, and projections of second order trigeminal neurons.

Project 5, like 4 and 3, will examine damage-induced changes in the organization of the trigeminal brainstem complex. In these experiments, however, the emphasis will be upon monoaminergic pathways, which are well known to influence the responses of trigeminal neurons.

Project 6 will have as its focus studies concerned with the effects of treatment with bovine brain gangliosides upon neuronal survival and the events which surround and may influence axonal regeneration by surviving neurons. A parallel series of experiments will also examine the effects of gangliosides upon trigeminal ganglion cell survival and neuritogenesis *in vitro*.

[317] Microdialysis Membranes for Chronic Studies

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Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health

Purpose/Methodology—During Phase I research of this project, microdialysis fibers were surface-modified to impart “biocompatible” surfaces (i.e., surfaces which were not neurotoxic and were not fouled by protein adsorption and cellular in-growth).

Results—*In vitro* testing of these fibers did not reveal any toxic effects on neurons or astrocytes. Although proteins did adsorb onto the membranes in these cultures, and some cellular infiltration was noted *in vitro*, occlusion of the membranes did not occur *in vitro*. In fact, the best surface-modified membranes, when implanted in striatum of rats, gave stable basal dopamine recoveries over a 13-day period. This is potentially a major breakthrough for chronic microdialysis given in previously-published results, and the widely-held belief that long-term implantation of dialysis membranes is not possible.

Future Plans—Phase II research will expand upon the results of Phase I. Three major sets of experiments are planned: 1) chronic monitoring of basal dopamine levels; 2) histological time course evaluation of the tissue changes around the dialysis fibers; and, 3) demonstration of end-use pharmacological testing. In addition, the production of second-generation probes, which will improve upon those currently available and broaden the scope of microdialysis applications, will be investigated.

Implications—The proposed research, on chronic microdialysis, surface modification, and biocompatibility, will greatly enhance the range of applications and utility of the microdialysis technique. Long-term neurophysiological and pharmacological studies will become possible. In addition, the inflammatory and foreign body responses caused by microdialysis fibers, which can distort findings even in acute experiments, will be avoided.

[318] Neural Pathways Involved in Tactile Discrimination

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Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health

Purpose—The proposed research is part of a project whose long-term goal is to add to our understanding of the tactile information processing capabilities and limitations of the somatosensory system, especially those neural regions and systems responsible for processing tactile information derived from mechanical stimulation of the glabrous surfaces of the hand.

Methodology—This project will examine the functional properties and stimulus-response relationships of single neurons of three spinal pathways which project, directly or indirectly, to the thalamic ventrobasal complex: the spinocervical tract, the postsynaptic dorsal column system, and the spinothalamic tract. Microelectrodes will be used to record extracellular activity of cell bodies or fibers in response to controlled mechanical stimulation of the glabrous skin of the raccoon's forepaw. Neurons will be identified as belonging to one of these three systems

by antidromic electrical stimulation of the appropriate region of spinal cord or brain stem.

Specific parameters to be examined include modality and adaptive properties, absolute thresholds, and receptive field areas, as well as effects of controlled mechanical stimulus velocity, displacement, and force on both dynamic and static discharge. Neurons will be sought which display properties suggesting excitatory or inhibitory convergences, and which display properties of feature detectors (e.g., preferential response to edges or laterally moving stimuli). Properties of neurons of the three spinal pathways will be compared with each other, as well as with properties of both primary afferents and neurons of the cuneate nucleus and thalamic ventrobasal complex, previously studied in this laboratory.

Implications—These studies should contribute to our knowledge of the differential contribution of three major

somatosensory pathways to the processing of tactile information acquired by a behaviorally salient tactile organ system, the forepaw or hand, especially its glabrous surfaces. This, in turn, should provide information relevant

to the design of devices for the utilization of tactile information by individuals handicapped in other sensory modalities. Findings should also have neurological relevance to the differential diagnosis of spinal cord injury or disease.

[319] Multi-Detector Brain Analysis System (MDBAS) ---

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Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health

Purpose—The goal of this project is to develop, test, and validate the prototype of a new positron annihilation coincidence probe MultiProbe (formerly called the Positron Multi-Detector Brain Analysis System—PMDBAS). The MultiProbe includes significant new technology for: 1) MRI image registration; 2) low-cost time-of-flight resolution improvement; and, 3) improved computer-guided image region of interest (ROI) sampling.

Progress—The new MultiProbe technique can be applied to both positron tracers and with suitable alterations to single-photon emission computerized tomography (SPECT) tracers. The MultiProbe combines both image

mensuration of the size of the anatomical features, such as tumors, with measurement of their physiologic activity. It provides positron measurement capability at costs projected to be under 120% of positron emission tomography (PET) making it a viable supplement or replacement for PET in many types of studies.

It has application as a monitoring instrument necessary to observe tissue condition repeatedly over a long period of time. The system allows reduced radiation exposure and permits up to 50 fluorodeoxyglucose (FDG) scans per year versus a limit of 3 per year for PET. The design of the device also significantly reduces the time required to perform a single measurement.

[320] Cerebral Capillary Perfusion During Oxygen Lack ---

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Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health

Purpose—Cerebral oxygen delivery is controlled by both cerebral blood flow and the number of perfused capillaries. Control of the number of perfused cerebral capillaries, in contrast to cerebral blood flow, has not been extensively studied under oxygen supply-limited conditions. From our previous work, we know that only about half of the available cerebral capillaries are perfused at rest, and that this reserve can be utilized during oxygen supply stress. Both central and peripheral adrenergic neurons can alter cerebral oxygen delivery. Their influence on cerebral oxygen delivery appears more important under conditions of oxygen lack.

The primary hypothesis of this project is that central and peripheral noradrenergic neurons decrease cerebral oxygen delivery by reducing alterations in diffusion distance and cerebral blood flow during oxygen supply stress. We intend to study the effects of various means of

reducing oxygen supply (anemia, hypoxia, carbon monoxide, hypocapnia) on the perfusion of cerebral capillaries and sympathetic influence on the control of oxygen delivery in conscious rats. We also intend to study the relative importance of the cerebral capillary response to oxygen lack.

Methodology—To perform these studies, we have developed a method to determine perfused and total capillary density on a regional basis in conscious rat brain. A fluorescent dye is injected to reveal the perfused vessels. The tissue is then stained to reveal the total network. This method, when coupled with measurements of cerebral blood flow with iodoantipyrine, and cerebral oxygen extraction with microspectrophotometry, will give a complete picture of the cerebral response to oxygen supply changes. The importance of peripheral sympathetic

innervation, central noradrenergic neurons and the arterial chemoreceptors in the control of cerebral capillary perfusion under conditions of reduced oxygen supply will be assessed. This will be determined in experiments involving ablation of the cervical sympathetic ganglia and arterial chemoreceptors.

Future Plans/Implications—We will study the effects of blockade of central and peripheral adrenoceptors. The

importance of changes in intercapillary distance on tissue oxygenation will also be assessed through increases and decreases in cerebral capillary density. Cerebral oxygen supply can be controlled at both the arteriolar and capillary level. Through study of the influence of the sympathetic nervous system on these two levels of control, we hope to gain a better understanding of its normal control of cerebral oxygen supply.

[321] Time-Resolved Spectroscopy of Hemoglobin in the Brain

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Sponsor: *National Institute of Neurological Disorders and Stroke, National Institutes of Health*

Purpose—The possibility of quantitative measurements of deoxyhemoglobin concentrations in the neonate and adult brain depends upon picosecond pulses of phase modulation spectroscopy that determine the optical path traveled by photons exiting the brain. Algorithms, based upon a program of milk and animal models, will be developed to permit localization of pathological states due to brain bleeding (i.e., hematomas or aneurysms). Thus, the possibility of nonradioactive, nonmagnetic, nonconfining studies based upon innocuous low-powered

deposition near red illumination on the surface of the head is the general goal of these studies.

Implications—These developments can lead to a new technology of quantitation and localization of normal and pathological levels of deoxyhemoglobin in the human brain. It is believed that this instrument has clinical applications and safety aspects that would allow it to be used wherever needed in research and clinical studies.

[322] Motor Control Systems in the Spinal Cord

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Sponsor: *National Institute of Neurological Disorders and Stroke, National Institutes of Health*

Purpose—This project was designed to provide information about the structure and function of neuronal mechanisms in the mammalian spinal cord which produce and control movement. These mechanisms include: reflex pathways that convey sensory information from primary afferents to alpha motoneurons; interactions between different reflex pathways; modulation of information flow through reflex pathways by supraspinal descending systems; and the production of autonomous rhythmic activity by central pattern generators within the spinal cord.

Methodology—Electrophysiological, neuroanatomical, and computer modeling approaches were used. Recent work has emphasized examination of the modulation of transmission through excitatory cutaneous reflex pathways by the spinal central pattern generator for locomotion, in order to clarify the organization of spinal interneurons that control the basic patterning of muscle activation during locomotion in the cat.

[323] Techniques for Making Connections with the Nervous and Musculoskeletal Systems

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Sponsor: *National Institute of Neurological Disorders and Stroke, National Institutes of Health*

Purpose—This project is intended to develop techniques and instrumentation for the acquisition and processing of neuroelectric signals from the central and peripheral nervous system in acute and chronic neurophysiological preparations. Because of this laboratory's continuing interest in sensorimotor neural activity during unrestrained move-

ments, the project also includes development and fabrication of chronically implantable mechanical transducers, catheters, and connectors. The development of computer programs of general utility for acquisition and analysis of neuroelectric and mechanical records is also included, as well as the development of neuroanatomical material.

[324] Studies in Neuromuscular and CNS Diseases and Their Experimental Models

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Sponsor: *National Institute of Neurological Disorders and Stroke, National Institutes of Health*

Purpose—Immunocytochemical studies were conducted using specific antibodies to thymic peptides to investigate the interaction of the immune system with the central nervous system (CNS), and peripheral nervous system (PNS).

Results/Implications—Thymosin-beta 4, an immunomodulating thymic polypeptide, was found to be a common antigen shared by macrophages, dendritic lymphoid cells, and the myelin-producing cells in the CNS (oligodendrocytes) and the PNS (Schwann cells).

Prothymosin (a nuclear protein), and thymosin-alpha 1 were found present in astrocytes of normal human brain tissue and could play a role in cell proliferation and gliosis.

The IgM of certain patients with paraproteinemic polyneuropathies has been identified as a specific antibody to acidic glycolipids; intraneural injection of IgM in the sciatic nerve of the cat induced demyelination, suggesting a direct role in the pathogenesis of the neuropathy.

The nature of amyloid protein in patients with "sporadic" amyloid polyneuropathy was identified using

specific antibodies to amyloid proteins: point mutations and direct sequencing of prealbumin genes, the precursor protein, were studied in the amyloid tissue using the polymerase chain reaction.

The mechanism of inflammatory myopathy in monkeys with immunodeficiency (simian AIDS) caused by SRV-1 and SIV-1 retroviruses was studied. Antibodies to myoblasts in tissue culture did not exert a cytopathic effect in the muscle. The role of SIV-1 was similarly studied. The effect of aging on the neuromuscular system of monkeys from age 5 to 25 is being studied, with a detailed morphological and morphometrical analysis of their muscle and nerve biopsies.

The mechanism of muscle regeneration is being studied by examining markers on satellite cells (including the role of adhesion on molecules such as laminin, N-CAM, and ICAM). The monoclonal antibody Leu-19 (NKH) that identifies natural killer cells was found to share common antigenic determinants with the satellite muscle cells. NKH also stains regenerating muscle fiber, and could play a role in muscle regeneration.

[325] The Role of Artificial Sensory Feedback in the Restoration of Motor Control

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Sponsor: St. Maartenskliniek, Department of Research and Development

Purpose—Rehabilitation, for a large part, can be seen as a learning process during which patients must reacquire old skills (e.g., walking). Ample evidence exists that feedback plays a crucial role in this process. Most motor tasks performed in natural settings provide the patient immediately with known results. Since the patient with motor dysfunction often also has sensory problems, he is totally dependent on the therapist for information concerning the outcome of his attempts. This dependence is especially true during the first stages of therapy when the task is new, and the primary concern is to understand

what has to be done, and how. This project evaluates the usefulness of several forms of artificial sensory feedback in the first phase of therapy.

Methodology—Portable feedback devices are used which enable the patient to practice also in their home situation during the performance of daily life activities.

Progress—A series of N=1 studies have been performed with patients suffering from the consequences of peripheral neurological lesion.

[326] Pathophysiology of the Anemia of Chronic Renal Failure

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Sponsor: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; University of Washington

Purpose—This project seeks the reasons why erythropoiesis remains suppressed in the majority of maintenance dialysis patients. Several hypotheses are under study which address the possibility of inhibitors remaining in the patient's sera by not crossing the dialysis membrane, or that some aspect of treatment may independently lead to this problem.

Methodology—Studies will seek the presence of hypothesized inhibitors of erythropoiesis in uremic sera. Experiments will also seek to determine if repetitive red cell transfusions may cause the phenomenon, or if aluminum may have an inhibiting role in heme synthesis within bone marrow. The applicability of using a dialyzer membrane of greater porosity will be studied if the presence of inhibitors remaining in uremic sera is demonstrated.

Preliminary Results—It has been found that although a hypoproliferative anemia exists in all patients with chronic renal failure, some patients improve their anemia, though by an unknown means. In normal persons, it has been found that hypertransfusion and phlebotomy cause reciprocal changes in erythropoietin production and red blood cell production, though these effects may be absent or blunted during uremia.

Future Plans/Implications—If the basis for continued suppression of erythropoiesis during dialysis can be elucidated, it may point toward strategies to relieve this very serious consequence of kidney failure, or relieve what may be proven to be a serious side effect of treatment.

[327] PLEXUS: A Knowledge-Based System to Assist with the Diagnosis and Treatment Planning of Brachial Plexus Injuries

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Sponsor: None listed

Purpose—A knowledge-based system is being developed to assist neurologists and neurosurgeons with the diagnosis and treatment planning of patients with a brachial plexus injury (nerve injury in the neck). The reason for developing this system is the very intricate anatomy of the brachial plexus, and the relative unfamiliarity with the possibilities of modern neurosurgical techniques.

Progress—A knowledge-based system has been developed for diagnosis and treatment planning. This system uses production rules for a rough localization of the injury, and then uses a search algorithm to find the exact location of the injury. It has been clinically tested at two Dutch centers of expertise on the subject of brachial plexus injuries. In order to increase the acceptability of the system, improvements have been made to the explanation facilities, and a graphical user interface has been developed for data entry on computer. Work is also being done on more explicit modeling of the knowledge, by means of a formalism using objects and relations.

Results—The rule-based knowledge base has been tested clinically, and has shown to give correct advice for diag-

nosis and treatment plan in 80% of 15 cases. A double-blind test with the system has also been carried out. Although the number of test cases is quite small, we may conclude that the knowledge-based system has a good performance.

Future Plans/Implications—This rule-based system, with graphical interface, will be installed in two clinics for further testing. Modeling of the knowledge in objects and relations will be continued. And finally, a critiquing facility will be incorporated into the system to allow it to react to the physician's own ideas about the diagnosis and treatment plan.

Recent Publications Resulting from This Research

Explanation Improvement to Enhance Acceptance of the PLEXUS System. Van Daalen C, Jaspers RBM, Lecture Notes in Medical Informatics, in Proceedings of AIME 89, 38:286-295, J. Hunter et al. (Eds.). Berlin: Springer-Verlag, 1989.

Modelling the Rehabilitation of Brachial Plexus Injuries: The PLEXUS System. Jaspers RBM, Van Daalen C, Van der Helm FTC, J Med Eng Technol 13:114-118, 1989.

Medical Decision Support: An Approach in the Domain of Brachial Plexus Injuries. Jaspers RBM, PhD diss., Delft University of Technology, 1990.

B. Arthritis

[328] Biochemical Analysis of Synovial Activation in Joint Dysfunction

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Sponsor: VA Rehabilitation Research and Development Service (Project #A052-5RA)

Purpose—The purpose of this study was to answer the following questions: 1) Is synovial cell activation by cartilaginous or metallic particles, metal ions and interleukin-1 mediated by one of the "classical" second messengers, such as cAMP or Ca^{2+} ? 2) Are alterations in protein phosphorylation involved in synovial cell

activation by these mediators? 3) Is the synthesis of collagenase in response to these mediators correlated with changes in the abundance of mRNA for the collagenase gene? and, 4) Does synoviocyte activation by metal ions or metallic particles occur *in vivo* as well as *in vitro*?

Progress/Methodology—We have answered questions 2 and 3, and are now focusing on question 1. We have also begun the *in vivo* work on question 4.

To determine whether changes in protein phosphorylation occur during the cellular activation of synoviocytes, cultures of these cells were equilibrated with ^{32}P -orthophosphate for 3 hours. Cells were then washed and duplicate cultures treated with activators of interest for periods of time ranging from 1 minute to 1 hour. Following these incubations, cells were washed, lysed and their proteins separated by two-dimensional gel electrophoresis employing isoelectric focusing in the first dimension and sodium dodecyl sulfate polyacrylamide gel electrophoresis in the second. Radioactive spots of ^{32}P -labeled proteins were identified by autoradiography and comparisons made between the patterns of phosphoproteins in control and activated cells. As such autoradiograms contained over 800 different spots, comparison proved too complex for the naked eye. Autoradiograms were thus compared by computer. Such analyses confirmed that approximately 40 proteins became newly phosphorylated upon cellular activation, while the phosphorylation of several proteins was decreased upon activation.

Preliminary Results/Implications—Such changes in protein phosphorylation are best explained as a reflection of changes in the activities of one or more protein kinases. As a result, we are presently attempting to identify the kinase or kinases responsible. Best studied in this regard are protein kinases which are activated by cyclic nucleotides, Ca^{2+} alone, or phospholipids and Ca^{2+} . We have consequently devoted considerable effort to determining which, if any, of these might be involved in synovial cell activation. So far, we have been unable to implicate cyclic AMP, cyclic GMP or Ca^{2+} in this response. Furthermore, a detailed and extensive analysis of the possible role of protein kinase C, which depends upon Ca^{2+} and phospholipid for its activity, has failed to identify a role for this kinase in the activation of synoviocytes by the activators we are studying. This is a little surprising since phorbol myristate acetate, a chemical which strongly activates protein kinase C, also strongly activates synoviocytes. These studies are continuing. Of great potential interest is a new, membrane-bound kinase which we have recently identified. The activity of this

kinase appears to correlate with activation of the cells. We expect the characterization and analysis of this kinase to be a major focus of the remainder of this funding cycle.

Since proposing to study the abundance of collagenase mRNA in activated cells, we also have obtained a cDNA probe for the rabbit stromelysin mRNA. These studies have thus been expanded to include measurement of both collagenase and stromelysin mRNAs. Resting cells contain very low levels of both of these mRNA species. Following activation, there is a lag phase of approximately 3 to 5 hours, after which the abundances of both of these messages increase coordinately, reaching steady state levels after 12 to 24 hours. The messages are very stable, remaining at high abundance for at least 48 hours after the removal of the activator. Regardless of the activating agent (particles, interleukin-1, metals) there is always a correlation between the cellular synthesis of collagenase and stromelysin and the cellular abundances of the mRNAs coding for these enzymes. This indicates a pre-translational level of regulation. This is likely to reflect transcriptional regulation although alterations in message stability cannot be theoretically excluded.

Recent Publications Resulting from This Research

- Altered Patterns of Protein Phosphorylation in Articular Chondrocytes Treated with Interleukin-1 or Synovial Cytokines. Hukower KI, Georgescu HI, Evans CH, *FEBS Lett* 257:228-232, 1989.
- Approaches to Paramagnetic Separations in Biology and Medicine. Evans CH, Russell AP, Westcott VC, *Particulate Sci Tech* 7:97-109, 1989.
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- Cycloheximide Inhibits the Induction of Collagenase mRNA in Chondrocytes Exposed to Synovial Factors or Recombinant Interleukin-1. Lin CW et al., *Agents Actions* 27:445-447, 1989.
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C. Low Back Pain

[329] Low Back Pain Studies

Malcolm H. Pope, PhD; Martin H. Krag, MD; William Cats-Baril, PhD; Rowland Hazard, MD; Mary Moffroid, PhD; Steven Reinecke, MSME; David Wilder, PhD; Jerry Weisman, MSME; Antonia Clark, MS; Janice Clements, BS
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Sponsor: National Institute on Disability and Rehabilitation Research

Purpose—The Vermont Rehabilitation Engineering Center (REC), now in its second 5-year funding cycle, is committed to improving the prevention, treatment, and rehabilitation of low back pain through an integrated program of basic and applied research and information services. Specific objectives of the multidisciplinary center include: identification of risk factors for low back injury, pain, and disability; development of new measurement methods for diagnosis and research; evaluation of treatment programs and modalities; worksite assessment and modification; service delivery; information dissemination and training.

Affiliates of the Vermont REC include the Spine Institute of New England (formerly New England Back Center), which operates a comprehensive rehabilitation program for chronic low back patients; and Rehabilitation Technology Services, which provides service delivery to individuals with low back and other disabilities.

Projects/Progress—Several research projects are currently under way in the following areas:

1) **Prediction of Disability and Assessment of Rehabilitation Strategies.** *William Cats-Baril, PhD.* The REC continues its pioneering work on prediction of low back disability and construction of a comprehensive and accessible database on individuals with low back pain. A model has been developed that predicts disability outcome with 83% to 89% accuracy. A questionnaire based on this model is now being used to collect data at sites outside Vermont.

2) **Intervertebral Motion and Muscle Use Detection.** *Martin Krag, MD.* This project was designed to develop a methodology for characterizing intervertebral motion and muscle use patterns in the lumbar spine. The design and fabrication of necessary equipment and software have been completed; *in vivo* testing was begun in early 1990.

3) **Lifting Capacity.** *Rowland Hazard, MD.* A prototype device for measuring lifting ability has been developed. The device, which incorporates an assessment of

subject effort, promises to be a practical, reliable, and inexpensive means of determining lifting capacity for a wide range of occupational health practitioners.

4) **Exercise and Physical Conditioning.** *Mary Moffroid, PhD.* This project comprises several discrete studies designed to study the endurance, eccentric capability, and time to response (to postural shifts) of the muscles surrounding the lumbar spine. Long-range goals include designing effective measurement tools and treatment programs.

5) **Evaluation of Biofeedback in Lumbar Orthoses.** *Malcolm H. Pope, PhD.* Lumbosacral corsets are frequently prescribed for low back pain, although their effectiveness and mechanism of action have not been demonstrated. The project compares the effectiveness of auditory feedback, trunk inclination feedback, and EMG feedback; the project comprises design and testing of devices and two triple crossover studies.

6) **Seating Studies.** *Steven Reinecke, MSME.* A prototype lordotic CPM device has been designed; when incorporated in a typical office chair, it provides continuous motion in the lumbar region. The device is now being tested to determine its efficacy in minimizing back discomfort in both static (office) and vibrational (vehicle) seating environments. An adjustable sit-stand workstation has also been designed and is being tested by back-healthy subjects, as well as back pain patients, to assess its effect on subject fatigue, comfort, and productivity.

7) **Vibration Studies.** *David Wilder, PhD.* With a long-range goal of optimizing work environments that involve vibration, this project was designed to assess the relative contributions of various spinal support structures, seating components, and postures to fatigue and back pain. Worksite assessments are frequently performed to measure amounts of vibration and impact, and recommendations made to minimize their deleterious effects on the spine.

8) **Development of a Workload Assessment System.** *Jerry Weisman, MSME.* A Workload Assessment System is being developed to provide detailed information about

various biomechanical stresses in the workplace. Posture and load can be monitored continuously over the course of the day and analyzed to provide a picture of job task demands. The system will be used to assess job demands across several occupations, in Vermont and elsewhere.

9) Information Services: Publications. *Antonia Clark, MS. Public Relations. Janice Clements, BS.* The REC's Information Services Division comprises a variety of activities in the areas of I & R, publications, education and training, public relations, and research evaluation. A subject-specific bibliographic database on low back pain, called BACKFILES, has been developed to assist researchers and clinicians in locating information about low back research, treatment, and rehabilitation. The Vermont REC offers assistance in locating programs, and provides information search services.

Recent Publications Resulting from This Research

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- Design and Use of a Microcomputerized Real-Time Muscle Fatigue Monitor Based on the Median Frequency Shift in the Electromyographic Signal. Seroussi RE et al., IEEE Trans Biomed Eng 36(2):284-286, 1989.
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- Functional Restoration with Behavioral Support: A One-Year Prospective Study of Patients with Chronic Low Back Pain. Hazard RG et al., Spine 14(2):157-161, 1989.
- Internal Deformations of Intact and Denucleated Human Lumbar Discs Subjected to Compression, Flexion and Extension. Seroussi RE et al., J Orthop Res 7:122-131, 1989.
- Internal Fixation of the Lumbrosacral Spine: Experience with the Vermont Spinal Fixator. Krag MH, Chapter 22 in Lumbar Interbody Fusion: Principles and Techniques of Spine Surgery, P.M. Lin, K. Gill (Eds.). Rockville, MD: Aspen Publishers, 1989.
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- Trunk Muscle Electromyography and Whole Body Vibration. Seroussi RE, Wilder DG, Pope MH, J Biomech 22(3):219-229, 1989.
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- Rehabilitation of the Patient with Chronic Low Back Pain. Hazard RG et al., in Occupational Low Back Pain (2nd Edition), M.H. Pope et al. (Eds.). Chicago: C.V. Mosby Co., 1990.
- Rehabilitation Technology in the Workplace. Weisman J, in CRC Handbook of Rehabilitation Engineering, J. Leslie (Ed.). Boca Raton: CRC Press, 1990.
- Demographic Factors Associated with the Prevalence of Disability in the General Population: Analysis of the NHANES I Database. Cats-Baril WL, Frymoyer JW, Spine (accepted for publication).
- Identifying Patients at Risk of Becoming Disabled Due to Low Back Pain: The Vermont Rehabilitation Engineering Center Predictive Model. Cats-Baril WL, Frymoyer JW, Spine (accepted for publication).

[330] Development of a Computerized Documentation-Data Analysis System for Work Hardening

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Sponsor: National Institute on Disability and Rehabilitation Research; University of Illinois at Chicago

Purpose—The epidemic of disability resulting from low back pain continues to result in tremendous personal, social, and economic costs. The need for effective rehabilitation for low back pain patients has led to the proliferation of treatment programs. Unfortunately, we know relatively little about the effectiveness of rehabilitation for the low back pain patient. While rehabilitation programs accumulate volumes of data on low back pain patients, this data is generally not used for research. This problem will be addressed by developing a computerized,

clinical data-management system for work hardening, capable of managing a clinical database for research purposes while supporting the clinical documentation responsibilities of the rehabilitation therapist.

Methodology—A Documentation-Data Analysis System (D-DAS) has been designed to manage data for low back pain patients in work hardening rehabilitation programs. Demographic, initial evaluation, discharge evaluation, and follow-up variables have been selected to test specific

research questions and to support the program evaluation and documentation needs of the clinic. Forms and procedures for data collection have been developed and manuals have been written. Computer programs have been written using PC-SAS, a research-level statistical software package for the personal computer. These programs are being designed for data entry and documentation production from patient data collected at initial evaluation, discharge evaluation, and follow-up interview. D-DAS is being designed to have database, graphics, and statistical capabilities to manage patient data for research and program evaluation purposes.

Progress—Data collection instruments have been developed and are presently being used at two clinical sites. User-friendly data-entry screens have been developed for demographic and initial evaluation data from patients. D-DAS has been demonstrated to have the database

(e.g., electronic access to patient data), graphics, and statistical capabilities proposed. Using the “mail merge” capabilities of PC-SAS, a text-based report for the medical records has been developed which incorporates approximately 120 variables from a PC-SAS data set (e.g., patient name, referring physician, pain ratings, maximum weight lifted bilaterally, etc.). Pilot data has been collected on 25 patients and data entry and report production have been revised on the basis of this study.

Future Plans/Implications—Discharge and follow-up data entry screens and documentation reports are being developed. We plan to field test the software at one or two sites during the next few months. Data collection from three sites is planned for initial studies of predictors for return to work, as well as initial studies on the efficacy of work hardening treatment for the low back pain patient.

[331] Low Back Pain and Sciatica: Factors for Success of Therapy ---

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Sponsor: *National Institute of Neurological Disorders and Stroke, National Institutes of Health*

Purpose—Low back pain and sciatica are a complex clinical problem which causes great suffering, disability, and expense. The two constitute the greatest single clinical volume for both neurosurgery and orthopedics. Intradiscal therapy has recently been added to surgery and conservative care for management. Long-term effects of these drugs are not known, and definitive criteria to accurately predict success or failure of therapy are not defined. We plan to study a broadly-based population of patients to determine the factors associated with success (or failure) of the three major forms of therapy—surgery, intradiscal injection, and conservative care.

Methodology—Data from multiple centers representing neurosurgery and orthopedics will be accumulated on physical and X-ray findings, as well as social, demographic, and psychologic factors in these patients. Outcome will be evaluated for all treatments and correlated with these multivariant factors. Long-term evaluations will proceed for 5 years to compare the eventual outcomes, and the cost of care will be compared. The goal is to appropriately match outcome with treatment.

D. Swallowing Disorders

[332] Assessment of the Swallow Reflex in Patients with Dysphagia

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Sponsor: VA Rehabilitation Research and Development Service (Project #C443-RA)

Purpose—Our purpose has been to develop a nonradiographic method by which investigators can study certain aspects of swallowing. Ultimately, the results of this investigation will provide information to assist in determining appropriate rehabilitation techniques and evaluating progress for patients with dysphagia.

Of particular interest was application of the electroglottograph (EGG) to evaluation of certain temporal aspects of the pharyngeal stage of swallowing (swallow reflex). The EGG was developed as a noninvasive, electrical impedance method of measuring vocal fold contact during phonation and has not been used previously to measure the slow varying laryngeal movements that occur during swallowing.

Progress/Preliminary Results—We have studied the transfer function of two EGGs. The Fourcin EGG was analyzed first; at low frequencies, the output was found to be the derivative of the changes in neck impedance. This was not the case in the higher frequencies associated with the speech range; at higher frequencies, the EGG output directly represented the changes in neck impedance. We analyzed the Rothenberg EGG and found the output to be directly related to changes in neck impedance at all frequencies.

We made simultaneous measures of EGG output, oropharyngeal pressure, and videofluoroscopic images during swallowing. We found that the time during which the larynx was elevated always exceeded the duration of the pharyngeal pressure wave; the larynx began to elevate before or shortly after the initiation of the tongue-driving pressure, and always before the onset of the pharyngeal pressure wave. In all subjects, the pharyngeal pressure wave returned to baseline prior to the onset of laryngeal descent. From the EGG output, the onset of laryngeal movement and the time of maximum laryngeal elevation can be identified; however, placement of the electrodes is crucial.

The EGG can be used clinically as a method of evaluating delays in onset of initiation of the swallow reflex. It can also be used as a biofeedback device for

teaching patients how to perform the Mendelsohn maneuver (a swallowing posture that aids in prolonging opening of the cricopharyngeus muscle and in keeping the larynx elevated).

Two electromyographic studies have been performed. We first studied EMG activity in the superior pharyngeal constrictor muscle of normal subjects while they performed a series of reflexive and nonreflexive tasks. The nonreflexive tasks involved both speech and nonspeech activities, and the reflexive tasks involved swallowing and gagging. The reflexive tasks resulted in the greatest EMG activity. The gag produced about 60% of the activity produced by a swallow. The hierarchy of EMG activity was well-defined and suggested that certain voluntary tasks may be useful in reducing the potential for disuse atrophy in patients with pharyngeal constrictor weakness.

The second study looked at the duration of EMG activity in the thyroarytenoid, cricothyroid, and superior pharyngeal constrictor muscles of normal subjects during swallowing. Preliminary analysis indicates that EMG activity in the superior pharyngeal constrictor muscle is approximately 76 ms longer than EMG activity in the thyroarytenoid, and 94 ms longer than that from the cricothyroid muscle during swallow. Average duration of superior pharyngeal constrictor activity increased as bolus size increased. Thyroarytenoid activity was shorter for dry swallows but approximately the same for 10 cc and 20 cc bolus swallows.

We also studied the relationships between oral stage dysphagia, vallecular stasis, reduced hyoid elevation and movement, and position of the epiglottis in 330 dysphagic patients who had a swallow reflex. Multivariate analysis revealed significant relationships between all variables except oral involvement and deviant epiglottic function. Four types of epiglottic function that deviated from the description of normal position or motion during swallowing were identified.

Future Plans—We intend to begin development of a swallowing model.

Recent Publications Resulting from This Research

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Frequency Response of the Fourcin Electrolottograph and Measurement of the Temporal Aspects of Laryngeal Movement

During Swallowing. Perlman AL, Liang X, J Speech Hear Res (in press).

Use of the Electrolottograph for Measurement of Temporal Aspects of the Swallow: Preliminary Observations. Perlman AL, Grayhack JP, Dysphagia (in press).

[333] Swallowing Dysfunction in Nephropathic Cystinosis

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Sponsor: *National Institutes of Health*

Purpose—Nephropathic cystinosis causes renal failure in most patients at approximately 10 years of age. This can be prevented or retarded by cystine-depleting therapy with oral cysteamine. Patients who do not receive adequate cysteamine therapy can undergo renal transplantation, but the accumulation of cystine continues in other organs, resulting in various clinical abnormalities. We report age-related swallowing dysfunction in patients with nephropathic cystinosis.

Methodology—We studied 43 patients with cystinosis (24 who had received a renal transplant, and 19 who had not), 3 to 31 years of age. Oral motor function was assessed by a cranial-nerve oral sensorimotor examination, and an oral motor index was calculated for each patient. The oral phase of swallowing was assessed by ultrasonography, and the pharyngeal and esophageal phases were evaluated by videofluoroscopy.

Results—Approximately half the patients were slow eaters. Oral motor dysfunction, reflected by a higher oral

motor index, increased with age. Speech, oral structure and anatomy, and tongue and lip strength were particularly affected. Seven of nine patients, 21 to 31 years old, had abnormalities in all three phases of swallowing; the deficits were variable in younger patients. In 28 patients with cystinosis, the mean (\pm SD) duration of oropharyngeal swallowing, or a dry swallow (3.06 ± 1.06 seconds), was longer than in 14 normal subjects (1.89 ± 0.57 seconds; $P < 0.001$). This prolongation reflected impairment of the initiation phase of swallowing.

Implications—Swallowing dysfunction is a late complication of nephropathic cystinosis, probably related to muscular dysfunction. Changes in the consistency of foods, swallowing exercises, and long-term cysteamine therapy should be considered for patients with cystinosis who have difficulty in swallowing.

Recent Publications Resulting from This Research

Swallowing Dysfunction in Nephropathic Cystinosis. Sonies BC et al., New Eng J Med 323(9):565-570, 1990.

E. Vascular Disorders

[334] Postoperative Thromboembolism in Surgical Patients

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Sponsor: National Heart, Lung, and Blood Institute, National Institutes of Health

Purpose—This study encompasses a series of controlled prospective clinical trials designed to investigate the pathophysiology of thrombotic states and related conditions, and the pharmacology of new antithrombotic and hemostatic drugs. Two of the five trials are related to geriatric rehabilitation.

Methodology/Implications—One trial measures the degree to which venous thromboembolism can be prevented in elderly patients with fractures of the hip by administration of the heparin-like compound Organon 10172. A second trial examines the potential of activated

recombinant protein C to act as an antithrombotic agent in phlebography-diagnosed patients who are at high risk of developing postoperative venous thromboembolism: specifically, it investigates the efficacy and safety of the intraoperative and postoperative infusion of the protein which is prepared by recombinant DNA techniques, with a view to prevention of venous thrombosis in patients undergoing total hip replacement.

Recent Publications Resulting from This Research

Heparin for Prophylaxis of Venous Thromboembolism. Salzman EW, *Ann NY Acad Sci* 556:371-377, 1989.

[335] Basic and Clinical Studies of Coagulation Proteins

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Sponsor: National Heart, Lung, and Blood Institute, National Institutes of Health

Purpose—Warfarin is an established, effective prophylaxis against deep vein thrombosis in the setting of cemented total hip replacement, but its general use has been hindered by a perceived risk of increased bleeding complications. This study investigates whether the safer application of external pneumatic compression is as effective as warfarin anticoagula-

tion in prophylaxis after noncemented total hip replacement.

Preliminary Results—Preliminary observations indicate that thromboembolic disease in patients receiving noncemented prostheses is lower than in those receiving cemented prostheses.

[336] Emphysema—Physiologic Effects of Nutritional Support

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Sponsor: National Heart, Lung, and Blood Institute, National Institutes of Health

Purpose—In this investigation, the role of malnutrition in the pathogenesis of ventilatory dysfunction in emphysema will be assessed and the effectiveness of nutritional support in reversing this dysfunction determined. The chronic weight loss often found in patients with chronic

obstructive pulmonary disease (COPD) has an adverse effect on prognosis. There is a positive correlation of significant malnutrition with emphysema and, moreover, the degree of malnutrition is correlated with some aspects of pulmonary function.

Preliminary studies also suggest that malnutrition has an adverse effect on ventilatory muscle strength. In addition, weight loss and decrement in pulmonary function are not monotonic in these patients, but often occur as a "step change." In a recently completed pilot study, it was demonstrated that in a controlled setting these patients will gain weight, and that this weight gain is associated with improvement in peripheral and ventilatory muscle strength.

Methodology—Using a carefully controlled and randomized study design and monitored nutritional supplementation, the physiologic effects of nutritional repletion on the ventilatory function of malnourished emphysema patients will be determined. Complete pulmonary function testing, exercise, and 12-minute walk performance will be measured before and after nutritional intervention. In order to evaluate the effects of malnutrition and subsequent nutrition therapy on ventilatory muscle strength and function, maximal transdiaphragmatic, inspiratory and expiratory pressures will be measured before and after nutritional supplementation.

Handgrip strength, before and after nutritional intervention, will be used as an index of overall muscle

strength. By careful interviewing and close follow-up, the benefits of nutritional therapy will be examined for their effect on quality of life and requirements for hospitalization of these patients.

Implications—From the data collected in this investigation, it may be possible to develop a strategy by which nutritional intervention can be developed for COPD patients. If, as our pilot study suggests, muscle strength can improve with nutritional intervention, perhaps this could decelerate the predictable decline of ventilatory function in these patients.

Recent Publications Resulting from This Research

Body Weight in Chronic Obstructive Pulmonary Disease: The National Institutes of Health Intermittent Partial Pressure Breathing Trial. Wilson DO et al., *Am Rev Respir Dis* 139:1435-1438, 1989.

Oxygen Consumption of the Respiratory Muscles in Normal and Malnourished COPD. Donahoe M et al., *Am Rev Respir Dis* 140:385-391, 1989.

Metabolic Rate and Weight Loss in Obstructive Lung Disease. Wilson DO et al., *J Parenter Enteral Nutr* 14(1):7-11, 1990.

[337] Trial of Inspiratory Muscle Rest and Exercise in Chronic Obstructive Lung Disease

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Sponsor: National Heart, Lung, and Blood Institute, National Institutes of Health

Purpose—Dyspnea and disability in chronic obstructive lung disease (COLD) may be a result of inspiratory muscle dysfunction. If so, many patients with severe COLD may have chronic inspiratory muscle fatigue which can be treated by ventilatory muscle rest (VMR). A randomized controlled clinical trial has been developed to assess whether VMR will: 1) improve exercise performance; 2) alleviate the sensation of dyspnea; and, 3) improve measurable quality of life for patients with severe irreversible COLD.

Preliminary Results—Preliminary data, from uncontrolled trials, have shown substantial improvements

resulting from VMR. The effectiveness of this intervention in a more rigorously controlled investigation will be assessed before its diffusion renders a controlled study difficult. If successful, this new form of low-cost therapy may revolutionize the rehabilitation of patients with severe COLD.

Recent Publications Resulting from This Research

Effect of Nutritional Status on Exercise Performance in Patients with Chronic Obstructive Pulmonary Disease. Gray-Donald K et al., *Am Rev Respir Dis* 140:1544-1548, 1989.

[338] Training Level Versus Cardiac Adaptations in Patients with Coronary Heart Disease

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Sponsor: *National Heart, Lung, and Blood Institute, National Institutes of Health*

Purpose—Insufficient information is available for selection of the most appropriate exercise levels for training and rehabilitation of coronary heart disease (CHD) patients with varying degrees of severity. Several studies indicate that vigorous exercise can be safely performed, and that such training can elicit cardiovascular adaptations in selected CHD patients. In this study, the effects of low and high levels of regular supervised training are compared. Over a 2-year treatment period, cardiac adaptations among 200 patients with CHD documented by arteriogram or myocardial infarction will be examined. The hypothesis that exercise of appropriate intensity and duration will safely affect cardiovascular adaptations will be tested. Recruitment, training, and evaluation will take place at two affiliated clinical centers with long experience in cardiac rehabilitation.

Methodology—Eligible men will enter a pre-randomization program designed to identify and eliminate persons with adherence problems or poor motivation. Participants will be randomly assigned to high or low exercise groups, and will be evaluated periodically with two independent exercise techniques: supine ergometer exer-

cise and upright maximal exercise testing with gas exchange measurements. Both tests will include two-dimensional echocardiography pre- and post-exercise, as well as during exercise with the ergometer. Comparison of the value of the two exercise techniques will yield important clinical information. The major outcome assessed will be the change in exercise ejection fraction at one year. Additional observations reflecting ventricular function, myocardial oxygen delivery capacity, and metabolic alterations over time by treatment group will be noted.

Implications—Results of this study will contribute to a better understanding of long-term cardiac adaptations with different physical activity levels and possibly the efficacy of secondary prevention. Implications may be forthcoming for exercise prescriptions and patient evaluation in cardiac rehabilitation programs.

Recent Publications Resulting from This Research

Reproducibility of Two-Dimensional Exercise Echocardiography. Oberman A et al., *J Am Coll Cardiol* 4:923-928, 1989.

[339] Effects of Social Support on Recovery from Coronary Artery Bypass Graft Surgery

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Sponsor: *National Heart, Lung, and Blood Institute, National Institutes of Health*

Purpose—The purpose of this study is to enhance understanding of how different types of social support affect patients and their spouses following coronary artery bypass graft surgery (CABGS). Different types and sources of social support will be identified. The relationship of the type of support to health outcome and to spouses' psychological functioning will be determined.

Methodology/Preliminary Results—Data are being collected by interview within a short time prior to surgery

and at 1, 4, 12 months, and 2 years after surgery. The outcome will be evaluation of various parameters, including a profile of mood states, a sickness impact profile (for the patients), a symptom check list (for spouses), and marital satisfaction. Preliminary analyses suggest that social support is a moderate predictor of outcome for the spouse, but less so for the patient.

[340] Randomized Trial of Rehabilitation in Chronic Obstructive Pulmonary Disease

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Sponsor: *National Heart, Lung, and Blood Institute, National Institutes of Health*

Purpose—Rehabilitation programs for patients with chronic obstructive pulmonary disease (COPD) are common in clinical care throughout the western world. However, the efficacy of these programs has not been evaluated in randomized experimental studies that have followed patients longer than one year, or with outcome measures of important quality-of-life and psychosocial variables.

Progress/Methodology—In this trial, patients have been randomly assigned to comprehensive rehabilitation or to an education control group. The 119 patients participating in the program were evaluated prior to treatment, and after 2, 6, 12, 18, and 24 months. Outcome measures included both psychosocial and physiological variables. The psychosocial measures included a quality of well-being scale, measures of self-efficacy expectations, depression, and social support. The physiological measures included: pulmonary function tests, maximum exercise tolerance with measures of expired and arterial blood gases, and endurance exercise performance. In addition, perceived symptom ratings were taken with each exercise test. Data from the first year of follow-up have been evaluated. Some significant differences in outcomes between the comprehensive rehabilitation protocol and the patients' education protocol have been found.

Future Plans—It is proposed that this follow-up be extended for four additional years. Physiological variables will be evaluated every other year. Psychosocial measures will be taken each year. Using the quality of life outcome data, and data obtained on costs, we will construct a policy model evaluating the cost/utility of the various rehabilitation interventions.

Recent Publications Resulting from This Research

- Interday Reliability of Function Assessment for a Health Status Measure: The Quality of Well-Being Scale. Anderson JP et al., *Med Care* 27:1076-1084, 1989.
- Prediction of Maximum Exercise Tolerance in Patients with Chronic Obstructive Pulmonary Disease. (Abstract) Carlson DJ, Ries AL, Prewitt LM, *Chest* 96:232S, 1989.
- Pulmonary Rehabilitation. Ries AL, in *Manual of Clinical Problems in Pulmonary Medicine*, 3rd ed., R.A. Bordow, K.M. Moser (Eds.). Boston: Little, Brown & Co., 1989.
- Experimental Evaluation of Rehabilitation in Chronic Obstructive Pulmonary Disease: Preliminary Results on Exercise Tolerance and Health Status Outcomes. Toshima MT, Kaplan RM, Ries AL, *Health Psychol* 9:237-252, 1990.
- The Functional Effects of Social Relationships on Chronic Illness and Disability. Kaplan RM, Toshima MT, in *Social Support: An Interactional View*, 427-453, R. Sarason, I. Sarason, G.R. Pierce (Eds.). New York: John Wiley & Sons, 1990.
- The General Health Policy Model: An Integrated Approach. Kaplan RM, Anderson JP, in *Quality of Life Assessment in Clinical Trials*, 131-149, B. Spilker (Ed.). New York: Raven Press, Ltd., 1990.
- Pulmonary Rehabilitation. Ries AL, in *Geriatric Rehabilitation*, 107-120, B. Kemp, K. Brummel-Smith, J.W. Ramsdell (Eds.). Boston: College-Hill Press, 1990.
- A Comparative Study of Psychosocial Aspects of Adults with Cystic Fibrosis and Their Health Peers. Shepherd SL et al., *Chest* (in press).
- Adherence in the Patient with Pulmonary Disease. Kaplan RM, Ries AL, in *Pulmonary Rehabilitation: Guidelines to Success*, 2nd ed., J.E. Hodgkin, C.W. Bell, G. Connors (Eds.). Philadelphia: J.B. Lippincott Company (in press).
- Compliance in Medical Care: Reconsideration of Self-Predictions. Kaplan RM, Simon HJ, *Ann Behav Med* (in press).
- A General Health Policy Model: Applications of New Health Indicators in Studies of Aging. Kaplan RM, Anderson JP, in *Frailty in the Aged*, M. Ory, R. Weindrich (Eds.). New York: Springer-Verlag, Inc. (in press).
- Quality of Well-Being Before and After Ciprofloxacin Treatment of Pulmonary Exacerbation in Cystic Fibrosis. Orenstein DM et al., *Chest* (in press).

[341] Strategies for Promoting Adult Asthma Self-Management

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Sponsor: National Heart, Lung, and Blood Institute, National Institutes of Health

Purpose—Recently, a number of interventions have been initiated to promote self-management skills in adults with asthma. One of these, the Asthma Self-Management Program of the University of Alabama at Birmingham (UAB) is based on a patient self-help workbook that is combined with a specific protocol for training patients in its use, and for providing continuing encouragement to maintain self-management skills. This approach has been compared with a “usual care” approach in which subjects received a standard set of routinely available asthma education pamphlets. Because such pamphlets frequently are a part of normal care, it is important that interventions be compared to them rather than to the complete absence of patient education. The UAB Self-Management Program is information-rich and professionally labor-intensive, and evaluation efforts to date have involved only a single sample with a relatively short follow-up period (12 months). It is now appropriate to measure interventions that are more applicable in community practice settings and that involve longer follow-up periods.

Progress/Methodology—Another approach, the “Core Elements Intervention,” has been developed. The development of this protocol will be guided by existing data available on diffusion of innovations and will use “Focus Groups,” composed of physicians in community-based practice.

Procedures for enhancing medication adherence and appropriate self-monitoring with peak flow meters will be stressed, and the protocol will include systematic

follow-up procedures for encouraging and sustaining self-management skills.

A prospective randomized control study will be used to compare approaches over a 2-year period. Outcomes in the following areas will be assessed: 1) functional status; 2) knowledge of asthma; 3) adherence to recommended treatment regimens; 4) psychological influences on and reactions to asthma; and, 5) health care utilization.

Recent Publications Resulting from This Research

Assessing the Use of Metered Dose Inhalers by Adults with Asthma.

Manzella BA et al., *J Asthma* 26:223-230, 1989.

Improving Self-Management Skills of Adults with Asthma. Bailey WC et al., *Am Rev Respir Dis* 139:A144, 1989.

Learn Asthma Control in Seven Days: A Step-by-Step Guide Proven Effective in Research Studies Conducted at the University Hospital, UAB. Bailey WC, Manzella BA, Birmingham, AL: University of Alabama Board of Trustees, 1989.

Patient Characteristics Relevant to Effective Self-Management: Scales for Assessing Attitudes of Adults Toward Asthma.

Richards JM et al., *J Asthma* 26:99-108, 1989.

Controlling Asthma: A Brief Guide. Bailey WC, Manzella BA, Birmingham, AL: University of Alabama Board of Trustees, 1990.

Characteristics and Correlates of Asthma in a University Clinic Population. Bailey WC et al., *Chest* (in press).

Evaluation of the Efficacy and Cost Effectiveness of Health Education Methods to Increase Medication Adherence Among Adults with Asthma. Windsor RA et al., *Am J Public Health* (in press).

Peak Flow Meters: Are They Monitoring Tools or Training Devices? Reeder KP et al., *J Asthma* (in press).

A Randomized Trial to Improve Self-Management Practices of Adults with Asthma. Bailey WC et al., *Arch Intern Med* (in press).

[342] Application of Self-Management System to Asthmatic Adults

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Purpose—This investigation applies a self-management system to a population of adults with asthma. The foundation of the system, “Living with Asthma,” has been thoroughly tested with asthmatic children and, in pilot studies, with adults afflicted by the disorder.

Specific aims of the investigation include the following: 1) to thoroughly test the proven fundamentals in 120 adults afflicted with asthma; and, 2) to carefully test and evaluate the results using a number of dependent determinations, including paper-and-pencil instruments, pulmonary

physiology measures, activity restriction changes, medication scores, severity of attack measures, and socioeconomic changes.

Methodology—The basic design consists of a randomized control group in which patients with a confirmed diagnosis of asthma are randomly assigned to treatment or control conditions. All participants, however, will receive self-management training. All subjects will be followed for at least one year to determine the effectiveness of the program over time.

The data will be analyzed by appropriate parametric statistical procedures. At the conclusion of the investigation, all data will be reported so that it may effectively assist physicians in teaching self-management skills to their patients as a practical and cost-effective way to control asthma.

Recent Publications Resulting from This Research

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- The Effects of Antihistamines on Electrophysiological and Behavioral Measures of Cognition. Shucard DW, Creer TL, *J Allergy Clin Immunol* 84:284-285, 1989.
- The Effects of Theophylline on Cognitive and Behavioral Performance. Creer TL, McLaughlin JA, *J Allergy Clin Immunol* 83:1027-1029, 1989.

- Living with Asthma: Part II. Beyond CARIH. Creer TL, Kotses H, Reynolds RVC, *J Asthma* 26:31-52, 1989.
- The Practise of Behavioural Medicine. Creer TL, Wigal JK, 211-233, J. Wardle, S. Pearce (Eds.). London: The British Psychological Society and Oxford University Press, 1989.
- Psychological Problems Associated with Drug Therapy in Childhood Asthma. Creer TL, Gustafson KE, *J Pediatr* 115:830-855, 1989.
- A Reinterpretation of Psychologically-Induced Airways Changes: from Asthma to Activation. Kotses H, Hindi-Alexander M, Creer TL, *J Asthma* 26:53-63, 1989.
- The Revised Asthma Problem Behavior Checklist. Creer TL et al., *J Asthma* 26:17-29, 1989.
- Asthma. Creer TL, Reynolds RVC, in *Handbook of Clinical Behavioral Pediatrics*, M. Hersen, V.B. Van Hasselt (Eds.). New York: Plenum (in press).
- Asthma. Creer TL, Reynolds RVC, in *Psychological Aspects of Developmental and Physical Disabilities: A Casebook*. M. Hersen, V.B. Van Hasselt (Eds.). Beverly Hills, CA: Sage Publications (in press).
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- A Critique of 19 Self-Management Programs for Childhood Asthma: Part I. The Development and Evaluation of the Programs. Wigal JK et al., *Pediatr Asthma Allergy Immunol* (in press).
- A Critique of 19 Self-Management Programs for Childhood Asthma: Part II. Comments Regarding the Scientific Merit of the Programs. Creer TL et al., *Pediatr Asthma Allergy Immunol* (in press).
- The Effect of Suggestion on the Total Respiratory Resistance of Healthy Individuals. Wigal JK, Kotses H, Creer TL, *J Psychosom Res* (in press).
- The Prevalence and Costs of Childhood Asthma. Creer TL et al., *Am J Asthma Pediatr* (in press).

[343] Vibration Sense and Tarsal Disintegration

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Purpose—It is clear that loss of sensation is an important factor in the etiology of tarsal disintegration. However, the necessary degree and modality of this sensory loss have not been determined. The biothesiometer and Semmes-Weinstein monofilaments represent quantitative methods of sensory assessment which can detect small changes in sensory ability, even in situations where this ability is already significantly impaired. The purpose of this study was to assess the role of loss of vibration and pressure sensation in the etiology of the process of tarsal disintegration (TD).

Progress/Methodology—Twenty-one patients having tarsal disintegration were studied. The disintegration was graded as early (one bone involved, with or without arch

collapse); intermediate (more than one bone involved, with arch collapse); late (anatomic disconfiguration and ectopic calcification); or advanced (separation of fore- and hindfoot, or involvement of ankle mortise).

Measurements were first made of pressure sensation using Semmes-Weinstein monofilaments. Sensation was tested on the base of the great toe, and the first and fifth metatarsal heads (the most common sites for plantar ulceration). The highest threshold determined for these three areas was taken as the threshold for the foot. Patients unable to feel even the strongest stimulus (6.65 monofilament) were recorded as negative.

The biothesiometer was then used to assess vibration sensory thresholds on the base of the great toe and the medial malleolus. The amplitude of vibration of the

probe was increased until the patient could first feel sensation. This was repeated twice: the mean threshold for the great toe and the medial malleolus being added together to produce the value for each foot.

Both feet were measured using these criteria. The foot which had not undergone disintegration was used as a control.

Results—Of the 21 patients examined, 12 had early changes of TD, 6 were of intermediate, 2 of late, and 2 of the advanced variety of TD.

It was observed that the group with TD showed a significantly higher vibration threshold than the group having no changes of TD. Most of the involved feet (18 out of 21) had a threshold value above 12 microns. Thus, in a population of highly insensitive feet, vibration sensation is more severely impaired in those with TD.

The majority of feet in both involved and noninvolved subsets (18 out of 21, and 8 out of 15, respectively), were unable to detect even the strongest stimulus delivered by a Semmes-Weinstein monofilament.

On the whole, no correlation was observed between the duration of disease and sensory thresholds. However,

the majority of patients having disease of more than 10 years' duration had a threshold value of greater than 20 μ M.

No correlation was found between the stage of TD and loss of vibration or pressure sensation, because TD is also related to many other factors of mechanical stress and strains, injuries, infection, weightbearing, etc. This corresponds to the theory that the patterns of disintegration are determined by the posture of mechanical stress in an intact, but insensitive, foot. It is suggested that once a certain degree of sensory loss has occurred, the process may continue regardless of further sensory changes.

Implications—From this small study it is not possible to give information as to a threshold above which disintegration becomes more likely; but significantly, most of the involved feet had a threshold above 12 microns. It is suggested that such a group of patients might be at a higher risk of disintegration of the tarsus, and this should form the basis of a prospective study. Thus, vibration sense measurement using a biothesiometer may be a valuable clinical test in the investigation and follow-up of patients having insensitive feet, and who are at high risk of developing TD.

[344] Motor Units in the Tibialis Anterior Muscle Six Months After Self-Reinnervation

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Purpose—Motoneurons innervate skeletal muscle in a very precise manner during development. The purpose of this work is to study the specificity with which motor axons innervate muscle after complete lesions to the nerve.

Methodology—In the right and left hindlimb of seven adult cats, the nerve branch innervating the anterior compartment of the tibialis anterior (TA) was cut near the muscle and the epineurium resutured, with an attempt made to maintain the original orientation between the proximal and distal ends of the nerve branches. Six months after the nerve was cut and repaired, a single motor unit from the TA in each limb was characterized physiologically and subsequently depleted of its glycogen through repetitive stimulation of a functionally isolated ventral root filament. The location of glycogen-depleted motor unit fibers was mapped in cross-sections taken along the length of the muscle. The following anatomical

measurements were obtained for glycogen-depleted motor units: innervation ratio (IR), mean fiber cross-sectional area (CSA), and specific tension (ST). In addition, spatial analyses were performed to quantify the distribution of motor unit fibers within a single cross-section.

Progress/Results—During the process of self-reinnervation of the tibialis anterior, motor axons (especially the fast motoneurons) tended to innervate more muscle fibers than normal, resulting in large force-producing units. The motor unit fibers in these large units tended to be clustered in groups and had a greater number of adjacencies among motor unit fibers than is observed in normal units. In addition, the anatomical data revealed a strong correlation between maximum force and innervation ratio ($r=0.92$). A stepwise linear regression showed that innervation ratio was the primary determinant of the maximum force in a motor unit.